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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/797,244	03/10/2004	Scott F. Sneddon	2478.1002-016	2987

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/797,244	SNEDDON ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *7-14 and 33-52* is/are withdrawn from consideration.

5)☒ Claim(s) *5,6 and 53* is/are allowed.

6)☒ Claim(s) *1-4,15-32 and 54-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/10/04, 12/8/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group II, claims 1-6, 15-32 and 53-59 in the reply filed on 11/8/2004 is acknowledged. Claims 1-6, 15-32 and 53-59 will be examined to the extent they embrace the elected subject matter. Claims 7-14 and 33-52 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The traversal is on the ground(s) that instant invention (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility and that the amendment to claims to limit the ring bearing V to be pyridine would reduce the search burden. The traversal is found not persuasive for reasons of record. As for the traversal the following apply.

The restriction is based on the fact that instant application is a US application not a 371 pf a PVT entering the national stage. MPEP § 803, clearly set forth the criteria for restriction requirement of US application and these criteria are clearly stated in the previous office action as basis for making restriction requirement. To reiterate:

As per MPEP § 803,there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent or distinct as claimed and

(B) There must be a serious burden on the examiner if restriction is required.

Both these conditions are to be met with. Instant inventions fail to meet these criteria as stated in the previous office action. To repeat:

Criteria A:

Invention I, II, III and IV are independent and distinct from each other because they are directed to structurally dissimilar compounds that lack common core namely pyrazole bearing Group I-IV are independent and distinct from each other because they are directed to structurally dissimilar compounds that lack common core such as triazine vs pyrimidine vs pyrazine vs pyridine v core. Consequently, the groups have different classifications and require separate prior art searches. They can be made and used independently. Art, which may render obvious or anticipate one of the groups, would not necessarily do the same for the other group as evidenced by the references cited in the Information Disclosure Statement provided by the applicants. Each can support a patent, as the compounds of each group are capable of being utilized alone not in combination with other members listed in the Markush group. Placing all such compounds into the same claims is not proper to scientific classification as they are separately classified and require separate searches.

Criteria B

In addition, it is necessary to classify and search all the controlling hetero cores and such a search of all controlling heterocores would serious search burden given the limited time available for each application.

Thus instant inventions fail to meet both these criteria.

Contrary to applicants' urging, limiting to carbon does not alter the need for restriction requirement as both above criteria still apply. The instant inventions embraced in Group I-IV are still independent and distinct and would impose serious search burden.

Prior art searched and those cited in the Information Disclosures statement does not suggest that all these cores are equivalent. Furthermore, applicants have not provided any evidence that these cores are equivalent. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicants have not provided any such evidence and hence instant varying heterocyclic cores are treated as independent and distinct not equivalent.

Hence, the restriction requirement is deemed as proper.

As for applicants' urging that instant invention (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility, the traversal lacks factual support.

First of all, there is no a substantial structural feature disclosed as being essential to that utility in the instant claims. The V bearing can be either pyrazine or pyridine, the ring directly attached to the pyrazole can be either pyrimidino or triazine and the pyrazole ring itself can be substituted with a triazole as seen in claim 7. Thus, entire heterocores can be varied. Thus a substantial structural feature essential for the activity is lacking. The first criteria is not met

Secondly, both references cited in the Information Disclosures Statement as well as those found during prior art search show that the pyrazole compounds bearing a substituted heterocycles ring system to possess herbicidal activity.

Thus, the second criteria that instant inventions share a common utility are also not met with.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

References cited in the Information Disclosure Statement filed on 3/10/2004 and 12/8 /2004, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4,15-32 and 54-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following apply. Any claim not

specifically rejected is rejected as being dependent on a rejected claim and share the same limitation.

1. Claim 1, 54 and their dependent claims are indefinite as claim 1 and 54 include a label A in the variable ring directly attached to pyrazole. It is not clear what is intended. An appropriate correction is needed.

2. Recitation of "physiologically acceptable salts thereof" in claims 56 and 58, renders these claims indefinite, as it is not clear whether the claim is compound claim or composition claim with above said limitations. Note Markush recitation should be in alternate form and in singular.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-32, 55, 57 and 59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for rheumatoid arthritis sepsis , irritable bowel disease and multiple sclerosis, does not reasonably provide enablement for any or all TNF-α mediated disorders including those yet to be discovered as due to TNF-α. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Following reasons apply.

The instant claims 71-100 and 108 are drawn to "treating TNF-α mediated condition ". The scope of the claims includes not only any or all conditions but also those condition yet to be discovered for which there is no enabling disclosure. In

addition, the scope of these claims includes treatment of various diseases, which is not adequately enabled solely based on the inhibiting expression of TNF-α activity of the compounds provided in the specification pages 15-17. The instant compounds are disclosed to inhibit TNF-α activity and it is recited that the instant compounds are therefore useful in treating any or all diseases where TNF-α activity is implicated, for which applicants provide no competent evidence. Furthermore, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. That a single class of compounds can be used to treat all diseases embraced in the claims is an incredible finding for which applicants have not provided supporting evidence. Moreover many if not most of diseases such as, multiple sclerosis, AIDS, malignant diseases etc. are very difficult to treat and at present there is no known drug, which can successfully reverse the course of these diseases, despite the fact that there are many drugs, which can be used for "inflammatory condition". Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Graninger et al. Curr. Opin. Rhematol.

13(3) 209-13, 2001 (PubMed Abstract provided) and Shaw et al. Expert Opin. Investig. Drugs 9(7) 1469-1478, 2000 (PubMed Abstract provided).

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating diseases that require inhibition of TNF-α activity.

2) The state of the prior art: A very recent publication expressed that treating disease by the inhibition of TNF-α is still exploratory. See references cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all

condition and the state of the art is that the effects of inhibiting TNF-α activity are unpredictable and at best limited to modulation of rheumatoid arthritis.

6) The breadth of the claims: The instant claims embrace any or all condition including those yet to be related to expression of TNF-α activity.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of receptor-ligand interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Allowable Subject Matter

Claims 5, 6 and 53 would be allowable barring finding of any prior art in a subsequent search. Said claims would be allowable because prior art search in the related area did not teach or suggest the compound and specific method of use embraced in the instant claims 5,6 and 53.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (571) 272-0674. If Applicants are unable to reach Mukund Shah within 24-hour period, they may contact James O. Wilson, Acting-SPE of art unit 1624 at 571-272-0661.

The fax phone number for the organization where this application or proceeding is assigned (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Venkataraman Balasubramanian

Venkataraman Balasubramanian

2/3/2005